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**ATTORNEY DOCKET NO. 10030803-1**

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1631

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**Inventor(s): Srinka Ghosh**

**Serial No.: 10/798,538** **Examiner: Lori A. Clow**

**Filing Date: March 11, 2004** **Group Art Unit: 1631**

**Title: METHOD AND SYSTEM FOR MICROARRAY GRADIENT DETECTION AND CHARACTERIZATION**



**COMMISSIONER FOR PATENTS**
**P.O. Box 1450**
**Alexandria VA 22313-1450**

## TRANSMITTAL OF APPEAL BRIEF

**Sir:**

Transmitted herewith is the Appeal Brief in this application with respect to the Notice of Appeal filed on November 18, 2007.

The fee for filing this Appeal Brief is (37 CFR 1.17(c)) **$500.00**.

**(complete (a) or (b) as applicable)**

The proceedings herein are for a patent application and the provisions of 37 CFR 1.136(a) apply.

☐ (a) Applicant petitions for an extension of time under 37 CFR 1.136 (fees: 37 CFR 1.17(a)(1)-(5)) for the total number of months checked below:

| | | |
|---|---|---|
| ☐ | one month | $ 120.00 |
| ☐ | two months | $ 450.00 |
| ☐ | three months | $1020.00 |
| ☐ | four months | $1590.00 |

☐ The extension fee has already been filled in this application.

☒ (b) Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

Please charge to Deposit Account **50-1078** the sum of $500.00. At any time during the pendency of this application, please charge any fees required or credit any overpayment to Deposit Account **50-1078**, pursuant to 37 CFR 1.25.

A duplicate copy of this transmittal letter is enclosed.

☒ I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date of Deposit: January 24, 2008 **OR**

☐ I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Date of Facsimile:

Typed Name: Joanne Bourguignon

Signature: Joanne Bourguignon

Respectfully submitted,

Srinka Ghosh

By Robert W. Bergstrom

Robert W. Bergstrom
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Reg. No. 39,906

Date: January 24, 2008

Telephone No. 206.621.1933

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

| | |
|---|---|
| Applicant: | Srinka Ghosh |
| Application No.: | 10/798,538 |
| Filed: | March 11, 2004 |
| Title: | METHOD AND SYSTEM FOR MICROARRAY GRADIENT DETECTION AND CHARACTERIZATION |

| | |
|---|---|
| Examiner: | Lori A. Clow |
| Art Unit: | 1631 |
| Docket No.: | 10030803-1 |
| Date : | January 24, 2008 |

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## APPEAL BRIEF

Mail Stop: Appeal Briefs – Patents
Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This appeal is from the decision of the Examiner, in an Office Action mailed August 24, 2007, finally rejecting claims 1-25.

## REAL PARTY IN INTEREST

Agilent Technologies is the Assignee of the present patent application. Agilent Technologies, Inc., is a Delaware corporation with headquarters in Palo Alto, California.

## RELATED APPEALS AND INTERFERENCES

Applicant's representative has not identified, and does not know of, any other appeals of interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

## STATUS OF CLAIMS

Claims 1-25 are pending in the application. Claims 1-25 were finally rejected in the Office Action dated August 24, 2007. Applicants' appeal the final rejection of claims 1-25 which are copied in the attached CLAIMS APPENDIX.

## STATUS OF AMENDMENTS

No Amendment After Final is enclosed with this brief. The last Amendment was filed May 30, 2007.

## SUMMARY OF CLAIMED SUBJECT MATTER

### Independent Claim 1

Claim 1 is directed to a method for detecting a background intensity gradient within a microarray data set by: (1) computing convergence metrics (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19) for features (404 in Figure 4) within the microarray (402 in Figure 4) data set (Current Application, lines 3-22 of page 5); and (2) when the convergence metrics computed for a number of features are larger than a threshold value, determining that the microarray data set exhibits a background intensity gradient (Current Application, lines 28-34 of page 31) and outputting a numerical indication of the determined background intensity gradient to at least one of a user, a display, a memory, or a computer (Current Application, lines 12-13 and 18-19 of page 32).

### Dependent Claims 2-11

Claim 2 is directed to the method of claim 1 wherein a convergence metric is computed for each feature (404 in Figure 4) in the microarray data set (Current Application, lines 3-22 of page 5). Claim 3 is directed to the method of claim 1 wherein a convergence metric is computed for a selected number of features (404 in Figure 4) in the microarray data set (Current Application, lines 3-22 of page 5). Claim 4 is directed to the method of claim 1 wherein the convergence metric computed for each feature is a convergence metric related to a difference between mean and median pixel intensities within background regions of increasing size containing the feature (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19). Claim 5 is directed to the method of claim 4 wherein the convergence metric computed for each feature is proportional to a size of a background region containing

the feature with a greatest difference between the mean and median pixel intensity for pixels within the background region (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19). Claim 6 is directed to the method of claim 4 wherein the convergence metric computed for a feature is proportional to a size of a background region containing the feature with a greatest difference between the mean and median pixel intensity for pixels within the background region, when a difference between a largest difference between mean and median pixel intensity for pixels within a background region and a smallest difference between mean and median pixel intensity for pixels within a background region is greater than a threshold value, and otherwise the convergence metric computed for a feature is a size of the feature (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19). Claim 7 is directed to the method of claim 4 wherein the convergence metric computed for each feature is proportional to a size of a background region containing the feature with a difference between the mean and median pixel intensity for pixels within the background region near to, but not equal to, the size of a background region with a greatest difference between the mean and median pixel intensity for pixels within the background region (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19). Claim 8 is directed to the method of claim 4 wherein features are disk shaped, and the background regions of increasing size are annuli circumscribing the feature with increasing outer radii (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19). Claim 9 is directed to a method comprising forwarding, to a remote location an indication obtained by a method of claim 1 as to whether or not a microarray data set (Current Application, lines 3-22 of page 5) contains a background intensity gradient. Claim 10 is directed to a method comprising receiving from a remote location an indication obtained by a method of claim 1 as to whether or not a microarray data set (Current Application, lines 3-22 of page 5) contains a background intensity gradient. Claim 11 is directed to a computer program implementing the method of claim 1 stored in a computer-readable medium (Current Application, line 7 of page 20 to line 15 of page 32).

<u>Independent Claim 12</u>

Claim 12 is directed to a method for characterizing background intensity gradients within a microarray data set by: (1) computing convergence metrics (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19) for features (404 in Figure 4) within the microarray (402 in Figure 4) data set (Current Application, lines 3-22 of page 5);

and (2) when the convergence metrics computed for a number of features are larger than a threshold value (Current Application, lines 28-34 of page 31), grouping features with computed convergence metrics by position (Current Application, lines 26-31 of page 32) and characterizing a background intensity gradient corresponding to each group of features by an area of the microarray surface corresponding to the group and by a position of the group on the surface of the microarray and outputting a numerical indication of the characterized background intensity gradients to at least one of a user, a display, a memory, or a computer (Current Application, lines 12-13 and 18-19 of page 32).

Dependent Claims 13-19

Claim 13 is directed to the method of claim 12 further including characterizing a background intensity gradient corresponding to a group of features (Current Application, lines 26-31 of page 32) by an average computed convergence metric for the features of the group. Claim 14 is directed to the method of claim 12 wherein a convergence metric is computed for each feature in the microarray data set (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19). Claim 15 is directed to the method of claim 12 wherein a convergence metric is computed for a selected number of features in the microarray data set (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19). Claim 16 is directed to the method of claim 12 wherein the convergence metric computed for each feature is a convergence metric related to a difference between mean and median pixel intensities within background regions of increasing size containing the feature (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19). Claim 17 is directed to the method of claim 16 wherein features are disk shaped, and the background regions of increasing size are annuli circumscribing the feature with increasing outer radii (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19). Claim 18 is directed to the method of claim 12 further comprising forwarding, to a remote location a characterization of a background intensity gradient within the microarray data set (Current Application, lines 3-22 of page 5). Claim 19 is directed to a computer program implementing the method of claim 12 stored in a computer-readable medium (Current Application, line 7 of page 20 to line 15 of page 32).

<u>Independent Claim 20</u>

Claim 20 is directed to a microarray data set analysis system comprising: (1) a

stored image of a microarray; and (2) a processing entity that computes a convergence metric (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19) for features (404 in Figure 4) within the image of the microarray (402 in Figure 4) and, when the convergence metrics computed for a number of features are larger than a threshold value (Current Application, lines 28-34 of page 31), determines that a background intensity gradient is present in the image of the microarray, groups features with computed convergence metrics larger than a threshold value by position (Current Application, lines 26-31 of page 32), and characterizes a background intensity gradient corresponding to each group of features, and outputs a numerical indication of the characterized background intensity gradient to at least one of a user, a display, a memory, or a computer (Current Application, lines 12-13 and 18-19 of page 32).

Dependent Claims 21-25

Claim 21 is directed to the microarray data set analysis system of claim 20 wherein the processing entity characterizes the background intensity gradient corresponding to each group of features (Current Application, lines 26-31 of page 32) by one or more of an area of the microarray surface corresponding to the group of features, a position of the group of features on the surface of the microarray, and an average computed convergence metric for the group of features. Claim 22 is directed to the microarray data set analysis system of claim 20 wherein a convergence metric is computed for each feature in the image of the microarray (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19). Claim 23 is directed to the microarray data set analysis system of claim 20 wherein a convergence metric is computed for a selected number of features in the image of the microarray (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19). Claim 24 is directed to the microarray data set analysis system of claim 20 wherein the convergence metric computed for each feature is a convergence metric related to a difference between mean and median pixel intensities within background regions of increasing size containing the feature (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19). Claim 25 is directed to the microarray data set analysis system of claim 24 wherein features are disk shaped, and the background regions of increasing size are annuli circumscribing the feature with increasing outer radii (Figure 14 and Current Application, line 8 of page 17 to line 2 of page 19).

## GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. The rejection of claims 1-25 under 35 U.S.C. §112, first paragraph.

2. The rejection of claims 1-25 under 35 U.S.C. §103(a) as being unpatentable over Yakhini et al., U.S. Patent No. 6,768,820 B1 ("Yakhini") in view of Nagarajan et al., IEEE Transactions on Nanobioscience (2002) Vol. 1, No. 2, pages 78-84 ("Nagarajan").

## ARGUMENT

Claims 1-25 are pending in the current application. In an office action dated August 24, 2007 ("Office Action"), the Examiner finally rejected claims 1-25 under 35 U.S.C. §112, first paragraph and finally rejected claims 1-25 under 35 U.S.C. §103 as being unpatentable over Yakhini et al., U.S. Patent No. 6,768,820 B1 ("Yakhini") in view of Nagajaran et al., (IEEE Transactions on Nanobioscience (2002) Vol. 1, No. 2, pages 78-84) ("Nagajaran"). Appellant's representative respectfully traverses both the 35 U.S.C. §112, first paragraph rejections and the 35 U.S.C. §103(a) rejections of claims 1-25.

**ISSUE 1**

1. The rejection of claims 1-25 under 35 U.S.C. §112, first paragraph.

In an office action dated February 28, 2007, the Examiner, in a discussion of 35 U.S.C. §101 rejections of claims 1-25, stated:

> This rejection could be overcome by amending the claims to recite that a result of the method is "displayed" or "outputted" (e.g. output to a user, a display, a memory, or another computer, etc.), or by amending the claims to include a step of a physical transformation of matter (e.g. assay).

Although Appellant's representative does not believe that the 35 U.S.C. §101 rejections were well foundationed, proper, or valid, Appellant's representative nonetheless elected to amend the claims, according to the Examiner's proposal, in an amendment filed May 29, 2007, rather than argue the 35 U.S.C. §101 rejections, in the interest of expediency. Appellant's representative inserted the language requested by the Examiner nearly word-for-word. In the current Office Action, the Examiner rejected claims 1-25 under 35 U.S.C. §112, first

paragraph, because Appellant's representative failed to provide support for the newly added claim limitations, and the Examiner further stated that no support "is apparent in the disclosure as originally filed." Appellants representative had assumed that, because the Examiner proposed the claim amendments, the Examiner was aware of the support for the suggested amendments.

Unfortunately, many bioinformatics patent applications are directed to life-sciences art groups, although bioinformatics is largely computational, in nature, and the life-science art groups appear to lack familiarity with computing, computer science, and quantitative techniques, in general. Had the Examiner read the C++-like pseudocode description of one embodiment of the present invention, the Examiner would have discovered the *for*-loop on lines 9-10 of the routine "computeRadiiOfConvergence" that is provided on lines 4-15 of page 32 of the current application. In the following statement, the current application refers to this pseudocode routine, as follows:

> The above function computes the convergence metric *X* for each feature in the image of the microarray via a call to function member "computeRadiusOfConvergence" and stores each converted convergence metric *X* into the two-dimensional array "radii."

Those familiar with computer science understand that a two-dimensional array declared in a C++ routine represents a portion of a computer memory. The current application is replete with statements and descriptions of execution of implementations of the current invention in microarray scanners and computer systems. Those familiar with computer science well understand that execution of such implementations results in the storage of computed convergence metrics into a computer memory or, as stated in the amendments to the current claims, "outputting a numerical indication of the determined background intensity gradient to a memory or a computer." The current invention is clearly intended for users of microarrays and microarray scanners, for example as stated on lines 8-11 of page 6 of the current application:

> For this reason, designers, manufacturers, and users of microarrays and microarray scanners continue to seek improved and computationally efficient methods for detecting defects and damage reflected in background intensity gradients and images of microarrays.

Furthermore, it is well known, and well understood by those ordinarily skilled in the art, that microarray-derived data is generally made available to human users. For example, on lines 12-17 of the current application, the current application states:

> These signal intensities are processed by an array-data-processing program that analyses data scanned from an array to produce experimental or diagnostic results which are stored in the computer-readable medium, transferred to an intercommunicating entity via electronic signals, printed in a human-readable format, or otherwise made available for further use.

As is well known to those familiar with microarrays, microarray-based experiments and assays, "[o]ptical, radiometric, or other types of scanning produce an analog or digital representation of the array as shown in Figure 7" (Current application, page 4, lines 23-25). In fact, the current application is replete with support for the claim amendments, originally proposed by the Examiner, directed to "outputting a numerical indication of the determined background intensity gradient to at least one of: a user, a display, a memory, or a computer."

The original 35 U.S.C. §101 rejections of claims 1-25 which motivated these claim amendments, currently rejected by the Examiner, are not well founded, in Appellant's respectfully offered opinion. Processes are entirely patentable subject matter under 35 U.S.C. §101. The analysis of patentability of claimed inventions involving computational methods involves determining whether the claimed subject matter is an abstract idea and, if so, whether or not the abstract idea is nonetheless patentable under various judicial exceptions. However, a method for computing a background intensity gradient within a microarray data set that computes "convergence metrics for features within the microarray data set" is most decidedly not an abstract idea. Abstract ideas compute nothing. Abstract ideas also do not make determinations about the presence of background intensity gradients based on whether or not computed convergence metrics are larger than a threshold value, as clearly claimed in claim 1.

**ISSUE 2**

2. <u>The rejection of claims 1-25 under 35 U.S.C. §103(a) as being unpatentable over Yakhini et al., U.S. Patent No. 6,768,820 B1 ("Yakhini") in view of Nagarajan et al., IEEE Transactions on Nanobioscience (2002) Vol. 1, No. 2, pages 78-84 ("Nagarajan")</u>.

<u>Claim 1, Representative of the Current Claims</u>

Claim 1 of the current application is representative of the current claims. Claim 1 is provided below, for the reader's convenience:

1. A method for detecting a background intensity gradient within a microarray

data set, the method comprising:

computing convergence metrics for features within the microarray data set; and

when the convergence metrics computed for a number of features are larger than a threshold value,

determining that the microarray data set exhibits a background intensity gradient; and

outputting a numerical indication of the determined background intensity gradient to at least one of: a user, a display, a memory, or a computer.

Claim 1 clearly claims "computing convergence metrics for features within the microarray data set." The current application provides a very detailed definition of term "convergence metric," in several different places in the current application. For example, on lines 8-17 of page 17 of the current application, the current application states:

> One useful metric that can be calculated for selected features within the image of a microarray is the convergence metric $\chi$. Figure 14 illustrates calculation of the convergence metric $\chi$ for the central features of the subregions illustrated in Figures 12 and 13. The convergence metric $\chi$ is defined as the outer radius of the annular background region surrounding a disk-shaped feature, the semimajor or semiminor axis length of the outer ellipse of an elliptical background region surrounding an elliptical disk-shaped feature, or the half width of a rectangular background region surrounding a rectangular shaped feature, having the greatest difference between a computed average background-pixel intensity and the median background-pixel intensity within the annular or rectangular background median. Alternative convergence metrics are possible, including converge metrics related to the above-described convergence metrics by constant multipliers, as well as the lengths of other types of mathematical features correlated with background region areas. The convergence metric $\chi$ is computed by computing the difference between the mean and median background-pixel intensities in background regions of increasing radius or half width about a particular feature, and then selecting as the convergence metric $\chi$ the radius of the background region for which the computed difference between the background-pixel average intensity and background-pixel median intensity is greatest. However, when the average/median-background-pixel-intensity difference computed for background regions of increasing radius or half widths do not show significant increase or decrease, then the convergence metric $\chi$ is defined to be the radius or half width of the feature.

A very detailed and precise implementation of a routine to compute a convergence metric is provided in the C++-like pseudocode routine "computeRadiusOfConvergence" provided in the current application from line 23 of page 29 to line 10 of page 31, followed by a thorough and precise English-language description of the computation of the convergence metric on

lines 11-34 of the current application.

Claim 1 additionally claims "when the convergence metric is computed for a number of features that are larger than a threshold value, determining that the microarray data set exhibits a background intensity gradient." Implementation of a threshold-based consideration is shown on lines 70-71 of the routine "computeRadiusOfConvergence" provided in the current application beginning on line 23 of page 29 of the current application and continuing to line 10 of page 31 of the current application. This is described, in text, in the final sentence of page 31 of the current application, from line 28 to line 34.

All of the independent claims 1, 12, and 20 include the limitations of "convergence metric" or " convergence metrics" and "background intensity gradient" or "background intensity gradients," and all recite a threshold-based determination of whether or not a background intensity gradient is present. Thus, claim 1 is representative of the independent claims of the current claim set. The following discussion focuses on claim 1, but is equally applicable to independent claims 12 and 20. Because all of the dependent claims necessarily include the limitations of the independent claims, the following discussion is applicable to all of the dependent claims, as well.

## Obviousness-type Rejections and Patent Application Examination

According to MPEP § 704.01:

> After reading the specification and claims, the examiner searches the prior art. The subject of searching is more fully treated in MPEP Chapter 900. See especially MPEP § 904 through § 904.03. *The invention should be thoroughly understood before a search is undertaken.* (emphasis added)

In Appellant's representative's respectfully offered opinion, when an Examiner has failed to read the application, has failed to understand the disclosure, or when the Examiner has insufficient technical and scientific background and education in the field of the invention to understand the disclosure, the examination process often descends to Office Actions containing unsupported and unsupportable conclusory statements, preparing responses to which represents an enormous waste of time and money.

According to MPEP § 706:

> The goal of examination is to clearly articulate any rejection early in the prosecution process so that the applicant has the opportunity to provide evidence of patentability and otherwise reply completely at the earliest opportunity.

Similarly, according to MPEP § 2142:

> The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.* ... noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."

In Appellant's representative's respectfully offered opinion, as discussed below, claim rejections that fail to even mention the limitations and elements of a claim and that refer to entire columns of an issued patent, without even a cursory attempt to indicate exactly what, in the cited reference, teaches, mentions, or suggests specific claim limitations and elements, falls far short of this standard.

According to MPEP § 2143:

> The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art.

In another words, the recent *KSR* decision has not changed the fact that, to establish a prima facie obviousness-type rejection, *the Examiner must find a teaching, mention, or suggestion of every element and limitation of a claim*.

35 U.S.C. §103(a) Rejection of Claim 1

In rejecting claim 1, the Examiner states:

> In regard to claims 1, 12, and 20, '820 teaches background intensity computations (column 2l, line 63 and 64).
>
> In regard to the metric computation in claims 1-3, 14, 15, 20, 22, and 23 '820 teaches the subtraction of background magnitudes (column 2, line 65) and the computation of feature positions (column 13 to column 14). The determination of single and all features is taught at column 8, lines 9-12).

These are the only two statements that Appellant's representative can find in the Office Action related to the final rejection of claim 1. The phrases "background intensity computations," "the subtraction of background magnitudes," "the computation of feature positions," and "the determination of single and all features," included in the Examiner's statement quoted above, do not occur in claim 1. The Examiner has failed to mention the

limitations and elements that do occur in claim 1, and has failed to point to any teaching, mention, or suggestion of those limitations in either cited reference. This rejection falls far short of the standard for obviousness-type rejections provided by MPEP §§ 706, 2142, and 2143, discussed above.

There is no occurrence of the claim phrase "convergence metric" in either cited reference. Apparently, the Examiner has decided to ignore the clear definition of the phrase "convergence metric" included in the current application, or has failed to have even noticed this definition. However, the Examiner is not free to ignore a clear definition for a claim term, and cannot arbitrarily assume some other meaning for well-defined claim language that is convenient for crafting an obviousness-type rejection. Again, the current application states that the "convergence metric $\chi$ is defined as the outer radius of the annular background region surrounding a disk-shaped feature, the semimajor or semiminor axis length of the outer ellipse of an elliptical background region surrounding an elliptical disk-shaped feature, or the half width of a rectangular background region surrounding a rectangular shaped feature, having the greatest difference between a computed average background-pixel intensity and the median background-pixel intensity within the annular or rectangular background median." Appellant's representative cannot find anything related to this definition anywhere in the cited references.

The Examiner points to lines 63-64 of column 2 of Yakhini, in which Yakhini states "extract data from the features and determine the magnitudes of background signals." There were, indeed, prior techniques for computing background-signal intensities, but this has nothing to do with the convergence-metric-based approach for "detecting a background intensity gradient," as claimed in claim 1. The cited passage of Yakhini does not teach, mention, or suggest anything at all concerning a "background intensity gradient," a "convergence metric," a threshold-based determination of the presence of a background-intensity gradient, or any other limitation or element of claim 1.

The Examiner points to line 65 of column 2, the entire contents of columns 13 and 14, and lines 9-12 of column 8 for teaching the many phrases, quoted above, from the Examiner's statements that do not occur in claim 1. Citing entire columns of a patent falls far short of articulating a basis for a rejection, as discussed above. These cited portions of Yakhini do not teach, disclose, mention, or suggest anything at all related to a "background intensity gradient" or a "convergence metric." Columns 13 and 14 contain text related to finding initial feature positions within an image of a microarray. This is quite unrelated to

the method claimed in claim 1. Lines 9-12 of column 8 describe computing a column vector for a feature - essentially summing columns of a two-dimensional matrix to produce a one-dimensional row, as shown in Figure 5. Again, this has nothing at all to do with a "background intensity gradient" or a "convergence metric," or any limitation or element of claim 1.

All of the current independent claims include language directed explicitly to "detecting a background intensity gradient within a microarray data set" and "computing convergence metrics." Neither Yakhini nor Nagarajan teaches, mentions, or in any way suggests a convergence metric or computation of a convergence metric to detect a background intensity gradient. The Examiner's rejection falls far short of the statutory, case law, and rule-based standards for 35 U.S.C. §103(a) rejections. Not only has the Examiner failed to point to anything in the cited references related to the limitations and elements of claim 1, the Examiner has failed to even mention or discuss the claim limitations and elements, instead discussing phrases and terms that do not occur in claim 1.

<u>Response-to-Applicant's-Arguments Section of the Office Action</u>

In the Response-to-Applicant's-Arguments section, on page 6 of the Office Action, the Examiner states:

> 1. Applicant argues that the current application is directed to identifying background-intensity gradients. Applicant states that a gradient is not scalar, but rather consists of vector quantities expressing the rate of change in background intensity. Applicant states that gradient-identification may be possible, but that Applicant has invented a particularly efficient method for identifying background-intensity gradients.
>
> This is not persuasive. Firstly, the Examiner is interpreting Applicant's arguments to mean that in the prior art, gradient-identification may be possible and therefore, Applicant has admitted that such a limitation exists in the prior art.
>
> Secondly, the argument that the prior art does not teach vector determination is not correct. 6,768,820 clearly teaches vector computation at column 4, lines 20-64 and column 7, lines 56-67 to column 8, lines 1-57, for example. '820 clearly contemplates background subtracted signals using vector calculations.

Appellant's representative is shocked by these statements. Appellant's representative provides, below, the portion of the previously filed response to which the Examiner apparently refers:

> With regard to the Examiner's 35 U.S.C. §103(a) rejections, Applicant's representative respectfully points out that neither Yakhini nor Nagarajan are concerned with identifying, or correcting for, background-intensity gradients. Instead, both Yakhini and Nagarajan employ background-correction methods that compute average, local backgrounds for each feature. In essence, both Yakhini and Nagarajan are concerned with computing the magnitude of the background intensity, which is a scalar value generally corresponding to some local, regional, or global average background computed for a microarray data set. By contrast, the current application is directed to identifying background-intensity *gradients*. A gradient is not a scalar value, but is instead a vector quantity expressing the rate of change of the background intensity in a particular direction within a microarray image. The task of computing background-intensity gradients is, in general, far more computationally intensive than computing local, regional, or global average backgrounds. The average backgrounds, as stated above, are scalar values that can generally be computed in a single pass. By contrast, gradients are directional values, and may require fairly sophisticated, non-local computation to identify, for example, the direction of greatest change, or the steepest gradient, at a given point in a microarray image. While many gradient-identification computational techniques may be possible, Applicant has invented a particularly efficient method for identifying background-intensity gradients using local, feature-based convergence metrics, rather than by using more computationally intensive, global analysis. Yakhini and Nagarajan do not discuss, mention, or suggest problems associated with background-intensity gradients, and neither reference, nor both references in combination, teaches, mentions, or suggests a method for identifying background-intensity gradients. Therefore, neither reference alone, nor both references in combination, can possibly teach the claimed method for identifying background-intensity gradients within a microarray data set.

Appellant's representative did not state that "a gradient is not scalar, rather it consists of vector quantities expressing the rate of change in background intensity." Appellant's representative instead stated: " A gradient is not a scalar value, but is instead a vector quantity expressing the rate of change of the background intensity in a particular direction within a microarray image." A gradient does not consist of vector quantities, as is well known to anyone familiar with basic, college-level mathematics. While this may appear to be a simple language error, Appellant's representative believes that this misstatement, along with additional evidence that the Examiner has not understood the current application, and may not have even read the current application, as discussed above with respect to the 35 U.S.C. § 112 rejections and as discussed further, below, indicates that the Examiner has failed to meet the standard for examination provided in MPEP § 704.01, discussed above.

Appellant's representative stated, in a previous response: "While many gradient-identification computational techniques may be possible, Applicant has invented a

particularly efficient method for identifying background-intensity gradients using local, feature-based convergence metrics, rather than by using more computationally intensive, global analysis." Appellant's representative was simply pointing out that, in addition to inventing a background-intensity-gradient based technique for extracting feature signals from a microarray data set, Appellant has also invented a particularly efficient method for background-intensity-gradient determination. Appellant's representative did not mention anything at all concerning prior art or the existence of limitations in prior art. Please note the language "*may* be possible." Appellant's representative is shocked that the Examiner, or any member of the USPTO, would seek to twist a purely scientific and technical statement into an imagined prior-art admission. This assertion by the Examiner cannot be supported by the above-quoted statement within the context of the paragraph in which it is included, cannot be supported by any reasonable parsing of the clear, English-language statement itself, and is completely unsupportable even as a legal trick or device. In Appellant's representative's respectfully offered opinion, these types of arguments have absolutely no place in any official statement or action produced by an administrative law agency. Examination is required to be based on established facts, not on conclusory statements or, worse, attempts to twist plain scientific and technical statements into prior-art admissions.

Finally, the Examiner's statement that "the argument that the prior art does not teach vector determination is not correct" again completely represents Appellant's previously stated position. *Neither Appellant nor Appellant's representative stated, either in the current application or in any response related to the current application, that "the prior art does not teach vector determination."* In fact, there is no occurrence of the phrase "vector determination" in the current application or in any response related to the current application. Appellant's representative has no idea what the Examiner means by this phrase. As any high-school student should well understand, vectors are well known. The cited portion of columns 4, 7, and 8 of Yakhini are directed to location of feature positions, and do not teach, mention, suggest, or have anything at all to do with computing background-intensity gradients. Apparently, having noticed the term "vector" in the cited passages, the Examiner somehow leapt to the conclusion that any mention of the term "vector" necessarily implies a discussion about "background-intensity gradients." Those familiar with basic mathematics and computer science well understand that vector can be used in a plethora of different fields and techniques, and that, while a "background-intensity gradient" may be an example of a vector, all vectors are by no means background-intensity gradients. The Examiner's apparent

position is as absurd as stating that, because threaded bolds are well known, any device that includes a threaded bolt is necessarily anticipated or obvious. Computing and employing background-intensity gradients in order to recover accurate, background-subtracted feature signals is, as far as Appellant and Appellant's representative know, unknown in the prior art. The first teaching, mention, or suggestion of computing background-intensity gradients using convergence metrics in order to recover feature-signal magnitudes occurs in the current application.

## CONCLUSION

In summary, the Examiner has completely failed to provide a proper and justified 35 U.S.C. §103(a) rejection of the current claims. Neither Yakhini nor Nagarajan teaches, mentions, or suggests anything at all to do with computing or using background-intensity gradients or convergence metrics, and both phrases are well defined in the current application and occur in each independent claim of the current claim set. The Examiner has, in fact, failed to point to any teaching, mention, or suggestion of any step or element of claim 1. The amendments to the current claims, previously proposed by the Examiner, are, in fact, well supported by the current application. Finally, the Examiner's statements in the "Response To Applicant's Arguments" section of the Office Action are inaccurate and misleading, and appeal to reveal a rather serious lack of understanding on the part of the Examiner of the subject matter of the current application and of basic, elementary mathematics.

Applicant respectfully submits that all statutory requirements are met and that the present application is allowable over all the references of record. Therefore, Applicant respectfully requests that the present application be passed to issue.

Respectfully submitted,
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## CLAIMS APPENDIX

1. A method for detecting a background intensity gradient within a microarray data set, the method comprising:

computing convergence metrics for features within the microarray data set; and

when the convergence metrics computed for a number of features are larger than a threshold value,

determining that the microarray data set exhibits a background intensity gradient; and

outputting a numerical indication of the determined background intensity gradient to at least one of: a user, a display, a memory, or a computer.

2. The method of claim 1 wherein a convergence metric is computed for each feature in the microarray data set.

3. The method of claim 1 wherein a convergence metric is computed for a selected number of features in the microarray data set.

4. The method of claim 1 wherein the convergence metric computed for each feature is a convergence metric related to a difference between mean and median pixel intensities within background regions of increasing size containing the feature.

5. The method of claim 4 wherein the convergence metric computed for each feature is proportional to a size of a background region containing the feature with a greatest difference between the mean and median pixel intensity for pixels within the background region.

6. The method of claim 4 wherein the convergence metric computed for a feature is proportional to a size of a background region containing the feature with a greatest difference between the mean and median pixel intensity for pixels within the background region, when a difference between a largest difference between mean and median pixel intensity for pixels within a background region and a smallest difference between mean and median pixel intensity for pixels within a background region is greater than a threshold value, and otherwise the convergence metric computed for a feature is a size of the feature.

7. The method of claim 4 wherein the convergence metric computed for each feature is proportional to a size of a background region containing the feature with a difference between the mean and median pixel intensity for pixels within the background region near to, but not equal to, the size of a background region with a greatest difference between the mean and median pixel intensity for pixels within the background region.

8. The method of claim 4 wherein features are disk shaped, and the background regions of increasing size are annuli circumscribing the feature with increasing outer radii.

9 A method comprising forwarding, to a remote location an indication obtained by a method of claim 1 as to whether or not a microarray data set contains a background intensity gradient.

10. A method comprising receiving from a remote location an indication obtained by a method of claim 1 as to whether or not a microarray data set contains a background intensity gradient.

11. A computer program implementing the method of claim 1 stored in a computer-readable medium.

12. A method for characterizing background intensity gradients within a microarray data set, the method comprising:

computing convergence metrics for features within the microarray data set; and

when the convergence metrics computed for a number of features are larger than a threshold value,

grouping features with computed convergence metrics by position; and

characterizing a background intensity gradient corresponding to each group of features by an area of the microarray surface corresponding to the group and by a position of the group on the surface of the microarray;

and outputting a numerical indication of the characterized background intensity gradients to at least one of: a user, a display, a memory, or a computer.

13. The method of claim 12 further including characterizing a background intensity gradient

corresponding to a group of features by an average computed convergence metric for the features of the group.

14. The method of claim 12 wherein a convergence metric is computed for each feature in the microarray data set.

15. The method of claim 12 wherein a convergence metric is computed for a selected number of features in the microarray data set.

16. The method of claim 12 wherein the convergence metric computed for each feature is a convergence metric related to a difference between mean and median pixel intensities within background regions of increasing size containing the feature.

17. The method of claim 16 wherein features are disk shaped, and the background regions of increasing size are annuli circumscribing the feature with increasing outer radii.

18 The method of claim 12 further comprising forwarding, to a remote location a characterization of a background intensity gradient within the microarray data set.

19. A computer program implementing the method of claim 12 stored in a computer-readable medium.

20. A microarray data set analysis system comprising:

a stored image of a microarray; and

a processing entity that

computes a convergence metric for features within the image of the microarray; and

when the convergence metrics computed for a number of features are larger than a threshold value,

determines that a background intensity gradient is present in the image of the microarray;

groups features with computed convergence metrics larger than a threshold value by position; and

characterizes a background intensity gradient corresponding to each group of features;

and outputs a numerical indication of the characterized background intensity gradient to at least one of: a user, a display, a memory, or a computer..

21. The microarray data set analysis system of claim 20 wherein the processing entity characterizes the background intensity gradient corresponding to each group of features by one or more of:

an area of the microarray surface corresponding to the group of features;

a position of the group of features on the surface of the microarray; and

an average computed convergence metric for the group of features.

22. The microarray data set analysis system of claim 20 wherein a convergence metric is computed for each feature in the image of the microarray.

23. The microarray data set analysis system of claim 20 wherein a convergence metric is computed for a selected number of features in the image of the microarray.

24. The microarray data set analysis system of claim 20 wherein the convergence metric computed for each feature is a convergence metric related to a difference between mean and median pixel intensities within background regions of increasing size containing the feature.

25. The microarray data set analysis system of claim 24 wherein features are disk shaped, and the background regions of increasing size are annuli circumscribing the feature with increasing outer radii.

## EVIDENCE APPENDIX

None.

## RELATED PROCEEDINGS APPENDIX

None.